

**REMARKS**

Claims 55-77 remain in this application.

The items below are responsive to the Examiner's rejections. Claims 55-60, and 70-77 are *currently amended* in this application. Claims containing "A" and "D" groupings have been amended to distinguish the subgroupings from one another. Claims 61-69 have been *previously presented*.

The paragraph numbers listed below correspond to the analogous paragraphs of this Office Action.

1. In reference to paragraph 1, the applicant has submitted a Supplemental IDS that addresses the objections raised by the Examiner.

2. Applicant acknowledges that the Examiner's rejection under 35 U.S.C. §112, second paragraph of claim 58 has been withdrawn.

3. Applicant acknowledges that the Examiner's rejection under 35 U.S.C. §102, anticipation, has been withdrawn.

4. Applicant acknowledges that the Examiner's rejections under 35 U.S.C. §112, second paragraph have been withdrawn.

5. Applicant acknowledges that the Examiner's rejection under 35 U.S.C. §112, first paragraph has been withdrawn.

6. Applicant acknowledges that the Examiner's rejection under 35 U.S.C. §112, first paragraph has been withdrawn.

7. Applicant acknowledges that the Examiner's rejections under 35 U.S.C. §112, second paragraph have been withdrawn.

8. Applicant acknowledges that the Examiner's rejection under 35 U.S.C. §102, anticipation, has been withdrawn.

9. Applicant acknowledges that the Examiner's rejection under 35 U.S.C. §102, anticipation, has been withdrawn.

10. Applicant acknowledges that the Examiner's rejection under 35 U.S.C. 102, anticipation, has been withdrawn.

11. Saito et al. (J. Enzyme Inhib.). This application does not claim D where D is C<sub>3</sub>-alkylene, substituted by OH, and subsequently an adjacent methylene unit (CH<sub>2</sub>) is isosterically replaced by CO. The definition of D allows for several options for substitution, but a combination of substitution and isosteric replacement is not described. Thus, D cannot represent -CH(CO<sub>2</sub>H)-CH<sub>2</sub>.

As defined in the claims 55, 60 and the claims dependent thereon, D is defined as follows (currently amended in the claims in Markush format):

*...D is selected from the group consisting of  
C<sub>3</sub>-C<sub>12</sub>-alkylene,  
a substituted C<sub>3</sub>-C<sub>12</sub>-alkylene which is substituted once or  
twice by C<sub>1</sub>-C<sub>6</sub>-alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkoxy or phenyl;*

*C<sub>3</sub>-C<sub>12</sub>-alkenylene,  
a substituted C<sub>3</sub>-C<sub>12</sub>-alkenylene which is substituted once  
or twice by C<sub>1</sub>-C<sub>6</sub>-alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkoxy or phenyl;*

*C<sub>5</sub>-C<sub>12</sub>-alkadienylene,  
a substituted C<sub>5</sub>-C<sub>12</sub>-alkadienylene which is substituted  
once or twice by C<sub>1</sub>-C<sub>6</sub>-alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkoxy or  
phenyl;*

*C<sub>3</sub>-C<sub>12</sub>-alkinylene,*

*a substituted C<sub>3</sub>-C<sub>12</sub>-alkinylene which is substituted once or twice by C<sub>1</sub>-C<sub>6</sub>-alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkoxy or phenyl;*

*C<sub>5</sub>-C<sub>12</sub>-alkeninylene,*

*a substituted C<sub>5</sub>-C<sub>12</sub>-alkeninylene which is substituted once or twice by C<sub>1</sub>-C<sub>6</sub>-alkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkoxy or phenyl;*

*and*

*C<sub>3</sub>-C<sub>12</sub>-alkylene, C<sub>3</sub>-C<sub>12</sub>-alkenylene or C<sub>3</sub>-C<sub>12</sub>-alkinylene, wherein, with the exception of the (G)-terminal methylene group in the C<sub>3</sub>-C<sub>12</sub>-alkylene, C<sub>3</sub>-C<sub>12</sub>-alkenylene or C<sub>3</sub>-C<sub>12</sub>-alkinylene, one to three methylene units in the C<sub>3</sub>-C<sub>12</sub>-alkylene, C<sub>3</sub>-C<sub>12</sub>-alkenylene or C<sub>3</sub>-C<sub>12</sub>-alkinylene are isosterically replaced by O, S, NR<sup>7</sup>, CO, SO or SO<sub>2</sub>, wherein R<sup>7</sup> has the same meaning as R<sup>6</sup>, but is selected independently thereof...*

From the definition of D, six possible options are available, but no combination of these options is taught. Claims 55, 60 and the claims dependent thereon are not anticipated by Saito. The claims of this application have been amended in the proper Markush format (MPEP 2173.05(h) and MPEP 803.02) to further establish the definition of D.

12. Koenig et al. (EP 477 499). The Examiner has combined two different definitions of D, one where D represents a substituted C<sub>3</sub>-C<sub>12</sub>-alkylene which is substituted once or twice by C<sub>1</sub>-C<sub>6</sub>-alkoxy and another where D represents C<sub>3</sub>-C<sub>12</sub>-alkylene, wherein one to three methylene units are isosterically replaced by NR<sup>7</sup>, CO, etc. In this application, D does not teach a combination of groups as suggested by the Examiner. Hence, D cannot be -CH(CH<sub>2</sub>O-t-Bu)-C(O)-NH-CH(CO<sub>2</sub>-t-Bu)-. The

definition of D is included in paragraph 11. Thus claims 55, 60 and the claims dependent thereon are not anticipated by Koenig.

13. Hashimoto et al. (Pharm. Res.). The Examiner has combined two different definitions of D similarly to the preceding paragraphs. In this application, D is not a combination of groups as suggested by the Examiner. Hence, D cannot be  $-\text{CH}(\text{CO}_2\text{H})-\text{CH}_2-$ . Thus claims 55, 60 and the claims dependent thereon are not anticipated by Hashimoto.

14. Kukkola et al. (Biorg. Med. Chem. Lett.). The Examiner's interpretation that D may represent  $-\text{CH}_2(\text{CH}_2-\text{SH})-\text{CH}_2-$  is not accurate. The Examiner has misinterpreted the definition of methylene unit because a methyl group does not contain a methylene unit, however merely represents a methyl group. An isosteric replacement of a methylene unit in a  $\text{CH}_3$  group is not possible and one cannot end up at mercaptomethyl ethylene for the definition of D. Kukkola does not anticipate the compounds and composition of the present invention. Claims 55, 60 and the claims dependent thereon are not anticipated by Kukkola.

15. Itoh et al. (WO 96/16981). D may represent a  $\text{C}_5$ -alkylene such as isopentylene. However, in the definition of D, either a  $\text{C}_3$ - $\text{C}_{12}$ -alkylene may be substituted by phenyl, or a methylene unit may be isosterically replaced by CO and  $\text{N}(\text{CH}_3)$ . A combination or substitution and isosteric replacement is not included in D's definition as defined in paragraph 11. Itoh et al. does not anticipate the compounds and compositions of the present invention.

16. Adams et al. (WO 96/22966). The Examiner stated that D for the present invention could be  $-\text{CH}(\text{iBu})-\text{CO}-\text{NH}-\text{CH}(\text{CH}_2-\text{CO}_2\text{H})-$ . The proposed chemical structure presented by the

Examiner has combined different definitions for D such as substitution in the CH<sub>3</sub> group by hydroxy group and isosteric replacement of methylene units by CO and NH. This combination however is not comprised by the present invention. Itoh does not anticipate the compounds and compositions of the current invention.

17. Myers et al. (J. Am. Chem. Soc.). This document discloses one single compound, [S-(R\*,R\*)]-N-(2-hydroxy-1-methyl-2-phenylethyl)-N-methyl-3-pyridine acetamide. This compound however has been specifically excluded in the amended claims. As a result, the teaching of Meyers et al. does not anticipate the compounds of the present invention.

18. Applicant acknowledges that the Examiner's rejection under 35 U.S.C. §102, anticipation has been withdrawn.

19. Audia et al. (WO 98/22494). The Examiner stated that the definition of D of the present invention comprises - CH(CH<sub>3</sub>)-C(O)-NH-CH(CH<sub>2</sub>-CH<sub>3</sub>)- from a combination of substitution and isosteric replacements. However, the definition of D does not disclose such a combination. Either D represents a substituted C<sub>3</sub>-C<sub>12</sub>-alkylene or it is exemplified by C<sub>3</sub>-C<sub>12</sub>-alkylene, wherein one to three methylene units may be isosterically replaced. The combination of substitution and isosteric replacement is not included. Hence, the teaching of Audia et al. cannot anticipate the compounds and compositions of the present invention.

20. Santangelo et al. (U.S. 5,760,241). The Examiner stated that the definition of D according to the present invention includes hydroxycarbonyl ethylene which is presented as a combination of substitution and isosteric replacement for C<sub>3</sub>-C<sub>12</sub>-alkylene in D which is not found in this invention's definition of D. The Examiner has misinterpreted the

definition of methylene unit because a methyl group does not contain a methylene unit, however merely represents a methyl group. An isosteric replacement of a methylene unit in a  $\text{CH}_3$  group is not possible and one cannot end up at hydroxycarbonyl ethylene for the definition of D. The teaching of Santangelo cannot anticipate compounds and compositions of the present invention.

21. Hayes et al. (WO 98/34111). The Examiner's interpretation that D may represent  $-\text{CH}(\text{CONH}_2)-\text{CH}_2-$  is not accurate. The Examiner has misinterpreted the definition of methylene unit because a methyl group does not contain a methylene unit, however merely represents a methyl group. An isosteric replacement of a methylene unit in a  $\text{CH}_3$  group is not possible and one cannot end up at aminocarbonyl-ethylene for the definition of D. Hayes does not anticipate the compounds and composition of the present invention.

22. Palmer et al. (U.S. 5,977,302). The Examiner's statement that D may be  $-\text{CH}(\text{CH}_2\text{OH})-\text{C}(\text{O})-$  is not correct. The Examiner has incorrectly combined the substitution of  $\text{C}_3-\text{C}_{12}$ -alkylene with an isosteric replacement of a  $\text{C}_3-\text{C}_{12}$ -alkylene. Additionally, the definition of the isosteric replacement does not allow an isosteric replacement for the (G)-terminal methylene group in  $\text{C}_3-\text{C}_{12}$ -alkylene. Palmer does not anticipate the compounds of the present invention.

23. Sham et al. (WO 97/21685). The Examiner states that the definition of D includes both  $-\text{CH}(\text{CH}_2-\text{Ph})-\text{CH}(\text{OH})-\text{CH}_2-\text{CH}(\text{NH}-\text{CO}-\text{O}-t-\text{Bu})-$  and  $-\text{CH}(\text{CH}_2\text{Ph})-\text{CH}(\text{OH})-\text{CH}_2-\text{CH}(\text{NH}_2)-$ . The Examiner has made his own invention by a combination of substitution and isosteric replacement. This combination, however, does not form part of the definition of D which may *inter alia* represent either substituted  $\text{C}_3-\text{C}_{12}$ -alkylene or  $\text{C}_3-\text{C}_{12}$ -alkylene wherein one to three methylene units are isosterically

replaced. In the definition of D, the substitution allows for a substitution by hydroxy or phenyl, but not for amino, whereas the isosteric replacement allows for  $\text{NR}^7$  or  $\text{CO}$ , but not for phenyl. Hence, the definition of D does not comprise the above two groups. The teaching of Sham does not anticipate the compounds, compositions and method of use of the present invention.

24. Abelman et al. (WO 96/19493). The Examiner's states that the definition of A comprises  $-\text{CH}_2-\text{CH}(\text{NH}_2)-$ . The Examiner has understood a methyl group as a hydrogen methylene group or hydromethylene group. This understanding however is in contrast to the general understanding of a methylene unit. Thus, the definition of A does not include amino ethylene. Abelman et al. does not anticipate the compounds and compositions of the present invention.

25. Hu et al. (U.S. 6,166,052). The Examiner has created an invention other than that described in this application through substitution of a methyl group for a methylene unit as described in the application. Accordingly, Hu cannot anticipate the compounds and compositions of the present invention.

Hu et al. is not prior art against this application under 35 U.S.C. 102(e). Hu has a priority date of March 11, 1998, whereas this application has a priority date of December 17, 1997.

26. Wu et al. (U.S. 6,191,166). The Examiner's statement that D may represent  $-\text{CH}(\text{CH}_3)-\text{C}(\text{O})-\text{NH}-\text{CH}(\text{CO}_2\text{Me})-$  is unclear. The Examiner has produced a combination of definitions of D which are different from the definition of D according to the present invention. Specifically, D allows for a substituted  $\text{C}_3-\text{C}_{12}$ -alkylene, substituted once or twice by  $\text{C}_1-\text{C}_6$ -alkoxy or it allows for a  $\text{C}_3-\text{C}_{12}$ -alkylene wherein one to three methylene

units in the C<sub>3</sub>-C<sub>12</sub>-alkylene are isosterically replaced by CO, or NR<sup>7</sup>. However, the definition of D in the present invention does not allow a combination of a substitution and an isosteric replacement. The teaching of Wu does not anticipate the compounds and compositions of the present invention.

27. Claim 73 has been amended to comply with 35 U.S.C. §112, first paragraph.

28. Claim 74 has been amended to comply with 35 U.S.C. §112, first paragraph.

29. Claim 75 has been amended to comply with 35 U.S.C. §112, first paragraph.

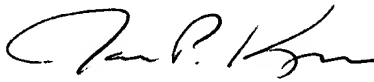
30. Claims 55, 56 and 58-75 have been amended to comply with 35 U.S.C. §112, second paragraph.

#### Conclusion

The Commissioner is hereby authorized to charge any additional fees which may be required in this application to Deposit Account No. 06-1135.

Respectfully submitted,

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